REMARKS

The Specification has been amended to correct certain informalities regarding the capitalization of terms which are trademarks or tradenames.

Non-elected claims 4-30 and 32-53 have been cancelled without prejudice. Claims 1-3 and 31 are pending.

Claim 1 has been amended to recite "wherein an increase in the expression level of the gene in the eosinophil cells of the test subject is indicative of an allergic disease." Support for this amendment can be found throughout the Specification and, in particular, at page 4, lines 10-15 and at page 4, lines 24-28.

The amended claims find support in the application as originally filed. Therefore, this Amendment does not add new matter. Further remarks are set forth below.

Priority

The Examiner has acknowledged receipt of papers submitted under 35 U.S.C. § 119(a)-(d) for a claim to foreign priority. However, the Examiner states that an English translation of the foreign priority document has not been received. Applicants supplied to the USPTO an English translation of the priority document on June 16, 2004 under Certificate of Mailing Procedure 37 C.F.R. 1.8. The OIPE of the USPTO acknowledged receipt of this and other documents on a postcard stamped with a receipt date of June 17, 2004. A copy of the postcard receipt is enclosed. Applicants respectfully request that the Examiner acknowledge Applicants' perfection of their claim to foreign priority.

Information Disclosure Statement

The Examiner has acknowledged receipt of the Information Disclosure Statements (IDSs) submitted on 6/17/2004 and 11/22/2004. However, the Examiner states the IDS submitted on 11/22/2004 has only been partially considered because a number of references cited therein (EP 1287019, EP1265628 and EP 1185647) were not supplied.

Please note that references EP 1287019, EP 1265628 and EP 1185647 were cited in the IDS submitted 6/17/2004 and not the IDS submitted 11/22/2004, as the Examiner states in the Office Action. 37 C.F.R. § 1.98(c) states that "[w]hen the disclosures of two or more patents or

publications listed in an information disclosure statement are substantially cumulative, a copy of one of the patents or publications as specified in paragraph (a) of this section may be submitted without copies of the other patents or publications, provided that it is stated that these other patents or publications are cumulative. " (MPEP 609, page 600-117, col. 2).

In the IDS submitted 6/17/2004, Applicants clearly stated that reference AM (EP 1287019) corresponds to reference AL (WO 01/87923), reference AO (EP 1265628) corresponds to reference AN (WO 01/70254) and reference AQ (EP 1185647) corresponds to reference AP (WO 00/77202), to indicate that the corresponding references were cumulative. Legible copies of WO 01/87923, WO 01/70254 and WO 00/77202 were provided as required. As EP 1287019, EP 1265628 and EP 1185647 are substantially cumulative with the aforementioned international applications, Applicants were not required to supply copies of the European patent publications.

Furthermore, according to Article 158(1) of the European Patent Convention, international publications published under Article 21 of the Patent Cooperation Treaty in one of the official languages of the European Patent Office (of which English is one) shall take the place of the publication of a European patent application (see enclosed copy of Article 158 of the European Patent Convention). In the present case, each of the three international publications are written in English and, as such, have taken the place of the corresponding European publications according to Article 158 (see, for example, enclosed cover page of WO 00/77202, stating that it takes the place of EP 118567). Applicants request the Examiner consider and indicate consideration of all three European patent publications.

Rejection of Claims 1-3 and 31 Under 35 U.S.C. § 112, First Paragraph

Claims 1-3 and 31 are rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement as the claims contain subject matter that was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. According to the Examiner, the Specification fails to enable a method for testing for *any* allergic disease as claimed. Furthermore, the Examiner states that the data supporting "significantly enhanced" expression of TR3 in atopic dermatitis samples are conflicting, citing a p-value for statistical analysis of greater than 0.05, which would be indicative of an insignificant finding. Finally, the Examiner notes that

while the invention may be enabled for measuring specific gene levels, it is not enabled for measuring specific protein levels as it is well known in the art that gene expression is not an accurate predictor of protein expression.

A Specification is presumed to be in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph. In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (emphasis added). Moreover, for the Examiner to sustain a rejection on the grounds of enablement, the Examiner must provide evidence that the claimed method could not be performed without undue experimentation. Thus, as stated by the Federal Circuit Court, "[a] conclusion of lack of enablement means that, based on the evidence...the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (emphasis added).

The Examiner has presented neither evidence nor a reasonable basis to question enablement of the claimed invention. No line of reasoning has been put forward to contradict Applicants' assertion that genes found to be differentially expressed in the eosinophils of atopic dermatitis patients would also be useful as markers in other allergic diseases. The MPEP states that, "[t]he presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors. To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims." (MPEP 2164.02, page 2100-187, col. 2, emphasis added). The MPEP also gives guidance as to enablement of a claimed genus, saying that "[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of the level of skill, state of the art, and information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation."

(MPEP 2164.02, page 2100-188, col. 1). In this case, the Examiner has not only failed to provide any grounds for doubting Applicants' assertions and findings, but has also failed to advance adequate reasons as to why, in view of the positive findings with respect to atopic dermatitis, a person skilled in the art could not extrapolate the disclosed method to other allergic diseases.

Applicants submit that the link between eosinophils and various allergic diseases is well-established, and was well-known in the art at the time the application was filed. Not only are eosinophils believed to mediate inflammatory and cytotoxic events associated with allergic disorders, including bronchial asthma (see enclosed Gleich GJ et al., 1993, Annu Rev Med 44:85-101 at page 93, paragraph 4 - page 95, paragraph 5 and Krogel C et al., 1994, Eur Respir J 7:743-760 at page 748, paragraph 2, col. 1- page 749, paragraph 1, col.1), rhinitis (see enclosed Howarth PH et al., 2000, Allergy 55:7-16 at page 7, abstract and paragraph 1, col. 1 and at page 12, paragraph 2, col.2) and urticaria, but they can also generate active substances like PAF, leukotriene C4, active species of oxygen and several cytokines which can lead to inflammation, bronchoconstriction and mucus hypersecretion, important components of airway allergic dysfunction (see enclosed Weller PF 1994, Curr Opinion Immunol 6:85-90 at page 86, paragraph 4, col.1- paragraph 1, col.2 and at page 87, paragraph 2, col.2 - page 88, paragraph 1, col.1). Accordingly, although eosinophil function may not be completely understood, it is well-established that eosinophils are prominent at sites of allergic reactions and, as such, are intimately connected with inflammation and allergy. Not only are eosinophils known to be present in inflammatory and allergic responses, but it has also been well-established that the number of eosinophils in the blood often rise above normal range during allergic reactions. Thus, genes having an expression level in eosinophils triggered by allergic disease that differs from their expression level in eosinophils in a normal state can serve as markers of allergic response in general. As demonstrated by Applicants, expression levels of TR3 and TINUR serve as markers of eosinophil activation and, therefore, these genes would find use as markers of any allergic disease, not atopic dermatitis alone.

Hence, it is clear from the references that it was well-known in the art at the time the application was filed that eosinophils' increased presence and activation are inextricably linked to allergic disease. Accordingly, one with skill in the art could easily extrapolate Applicants' invention to allergic diseases other than atopic dermatitis without undue experimentation.

Moreover, the Examiner has provided no reasons or evidence to the contrary. Therefore, the claimed invention is indeed enabled by the Specification.

With respect to the Examiner's assertion that the statistical analysis of the data is indicative of an insignificant finding in having a p-value of 0.0533, Applicants submit that the p-value of 0.0533 given for parametric multiple comparison using the Dunnett test in no way conflicts with Applicants' conclusion that there is a significant difference between TR3 expression in normal versus atopic dermatitis samples.

Parametric multiple comparison tests are known to be powerful when analyzing normally distributed data. However, it is also known that the statistical power of the tests significantly drops when applied to non-normally distributed data. In this case, data used for the statistical analyses comprised six to fifteen samples for each group and thus, there was a possibility that these data might not follow normal distribution. Therefore, the present inventors performed non-parametric multiple comparison tests, which do not depend on the distribution pattern of the data, to analyze differences in TR3 gene expression levels among patient groups (i.e., AL, MA and AS) and the control group (Nm). As a result, the p-values obtained by non-parametric Dunnett were in the range of 0.01-0.0339 and by non-parametric Tukey, in the range of 0.0189-0.0378 (see Specification at page 46, Table 7). These values are sufficiently low to statistically support the difference in TR3 expression levels among patient and control samples. Thus, we believe that one skilled in the art would readily and without doubt recognize that TR3 expression levels were significantly elevated in peripheral blood eosinophils of atopic dermatitis patients by the results of the non-parametric tests alone.

In applying parametric multiple comparison of the data using the Dunnett test for the sake of reference, Applicants happened to obtain a p-value of 0.0533, which just slightly exceeds the standard significance level of 0.05. As this parametric analysis was performed purely to provide supplemental data, this value of 0.0533 should not be construed as conflicting with the statistical results obtained by the non-parametric tests. Rather, it can be said that results of the parametric Dunnett analysis indicate that the data strongly support the results of the non-parametric analyses in that a p-value as close to the standard significance level as 0.0533 was obtained by parametric analysis even under conditions unfavorable to the test's ability to exert sufficient statistical power.

Concerning enablement of the claims to measure specific gene levels but not specific protein levels, Claim 1 has been amended to recite a method measuring and comparing the expression level of a "gene" encoding TR3 or TINUR in eosinophil cells of a test subject.

Therefore, in view of the knowledge in the art at the time the application was filed and the amendments to Claim 1, one with skill in the art would have no difficulty in making or using Applicants' invention for allergic diseases without undue experimentation, nor have difficulty ascertaining the significance of Applicants' findings based on the statistical analysis. Thus, Claims 1-3 and 31 meet the requirement of enablement under 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the rejection are requested.

Rejection of Claims 1-3 and 31 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-3 and 31 are rejected under 35 U.S.C. § 112, second paragraph as being incomplete for omitting essential steps, such omission amounting to a gap between steps. Specifically, the Examiner notes that the method recites "comparing expression level" without any specific guidelines for the comparison in the method.

Claim 1 has been amended to recite "wherein an increase in the expression level of the gene in the eosinophil cells of the test subject is indicative of an allergic disease" to give guidance as to how the comparison step relates to the method. As such, amended Claim 1 satisfies the requirement of 35 U.S.C. § 112, second paragraph. Claims 2, 3 and 31 are directly or indirectly dependent on Claim 1 and thus include the limitations of amended Claim 1 such that they also meet the requirement of 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of the rejection are requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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